Glutathione plays a crucial role in free radical scavenging, oxidative injury, and cellular homeostasis. Previously, we identified a non-synonymous polymorphism (P462S) in the gene encoding the catalytic subunit of glutamate-cysteine ligase (GCLC), the rate-limiting enzyme in glutathione biosynthesis. This polymorphism is present only in individuals of African descent. Presently, we report that this ethnic-specific polymorphism (462S) encodes an enzyme with significantly decreased *in vitro* activity when expressed by either a bacterial or mammalian cell expression system. In addition, overexpression of the 462P wild-type GCLC enzyme results in higher intracellular glutathione concentrations than overexpression of the 462S isoform. We also demonstrate that apoptotically stimulated mammalian cells overexpressing the 462S enzyme have increased caspase activation and increased DNA ladderingcompared to cells overexpressing the wild-type 462P enzyme. Finally, we genotyped several African and African-descent populations and demonstrate that the 462S polymorphism is in Hardy–Weinberg disequilibrium, with no individuals homozygous for the 462S polymorphism identified. These findings describe a glutathione production pathway polymorphism present in individuals of African descent with significantly decreased *in vitro* activity.